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Santé et Bien-être social Canada

# Health Protection and Drug Laws

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# Health Protection and Drug Laws

Health Protection Branch
Health and Welfare Canada

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# About This Booklet

The *Food and Drugs Act* and the *Narcotic Control Act* are the two pieces of legislation that govern the availability and use of drugs in Canada. The public and various interest groups often need clarification regarding the content of these acts. Questions may also arise concerning the need for portions of the legislation. Typical questions about drug laws in Canada are:

*Why do we have drug laws?*
*What are Canada's drug laws?*
*How are our drug laws implemented?*

This booklet answers these and other questions about drug laws in Canada. Please note, however, that it is not a step-by-step guide through the *Food and Drugs Act* and the *Narcotic Control Act*.

This booklet also describes the role of the Health Protection Branch in administering our drug laws, the processes involved in dealing with a wide range of drug issues, some of the major regulations applied to the various classes of drugs, and the reasons why those regulations have been developed.

The information is presented so that it can be easily understood, and subsequently used, by a number of interest groups—including professionals and students in health disciplines, consumer advocate groups, and students of consumer protection laws—in their dealings with the public, with governments at all levels, and with industry. To help the reader understand the information, a glossary of terms is provided.

Readers who would like more detail should use this booklet in conjunction with the Acts and their regulations. The reader may also wish to consult the reference publications listed at the back of this booklet. Further information about the role of Health and Welfare Canada with regard to drug laws may be obtained by contacting the Health Protection Branch offices listed at the back of this booklet.

# 1. Drug Laws— A Historical Perspective

## Purpose of Drug Laws

Drug laws help to ensure that all drugs used in Canada are safe, effective, and wisely administered. The *Food and Drugs Act* and the *Narcotic Control Act* govern the manufacture, distribution, advertising, and sale of drugs in Canada.

The *Food and Drugs Act* and the *Narcotic Control Act* evolved from earlier pieces of legislation known respectively as the *Inland Revenue Act* and the *Opium Act*. The more detailed technical requirements of the *Food and Drugs Act* and the *Narcotic Control Act* are described in their associated regulations.

## Evolution of the *Food and Drugs Act*

The *Inland Revenue Act* of 1876, which dealt primarily with the use of alcohol, did not define drugs. This legislation was the forerunner of the more effective *Adulteration Act* of 1884, which defined the terms *drug* and *adulteration*, and the conditions under which adulteration of a drug might take place. This Act was eventually repealed and replaced by the *Food and Drugs Act* of 1920. In 1953, the *Food and Drugs Act* was amended to control the manufacture, distribution, and sale of all drugs except narcotics.

Another piece of legislation, which was originally passed as a result of concern about the efficacy and safety of "secret-ingredient" drugs, was the *Proprietary or Patent Medicine (PPM) Act* of 1909. This act was revoked in 1977 and the drugs formerly listed under it are now governed by the *Food and Drugs Act*.

In the *Food and Drugs Act*, a drug is defined as any substance used in the diagnosis, treatment, mitigation, or prevention of a disease, disorder, or abnormal physical state, and in restoring, correcting, or modifying organic functions in humans or animals.

The *Food and Drugs Act* has the schedules listed below:

| | |
|---|---|
| Schedule A | List of diseases, disorders, and abnormal physical states that can be diagnosed and treated only by a medical practitioner. |
| Schedule B | List of publications containing drug standards considered official in Canada. |
| Schedule C | List of radiopharmaceuticals. |
| Schedule D | List of biologic drugs, including vaccines and blood products. |
| Schedule G | List of controlled drugs (e.g., stimulants, sedatives). |
| Schedule H | List of restricted drugs (e.g., LSD), with no medical use. |

## Evolution of the Narcotic Control Act

The *Opium Act* of 1908 prohibited the unauthorized importation and possession of gum or smoking opium. In 1911, the Act was expanded and became the *Opium and Drug Act*, which included other problem drugs such as cocaine and morphine. Amendments to the *Opium and Drug Act* were made in 1919 to accommodate import and export licences. As illicit trade in narcotics increased and more control became necessary, the act was changed again in 1920, becoming the *Opium and Narcotic Control Act*. The *Narcotic Control Act* of 1961 now controls the manufacture, distribution, and sale of the narcotic drugs listed in the Schedule to the Act.

## The Regulations

The *Food and Drugs Act* and the *Narcotic Control Act* contain broad statements regarding the safety, efficacy, and control of drugs. The more detailed technical requirements are outlined in the *Food and Drug Regulations* and the *Narcotic Control Regulations*. The Regulations have the same force and effect as the Acts and can be used as a means of rapidly updating the legislation.

# 2. Role of the Health Protection Branch

## Overview

The role of the Health Protection Branch (HPB) is to protect and improve the well-being of Canadians by identifying, assessing, and managing risks to human health. To achieve its goals, the HPB carries out a wide range of activities associated with

- the food supply;
- the availability, use, manufacture, and sale of drugs (including immunizing agents and biologics) and cosmetics; and
- the natural and technological environment, including medical and radiation-emitting devices, chemical products, and environmental contaminants.

As well, the HPB acts as a national centre for the identification, investigation, control, and prevention of communicable and non-communicable human disease. The HPB is involved in activities designed to control the spread of AIDS in Canada and to reduce the health, social, and economic effects of AIDS.

The organization of the HPB is shown in Figure 1.

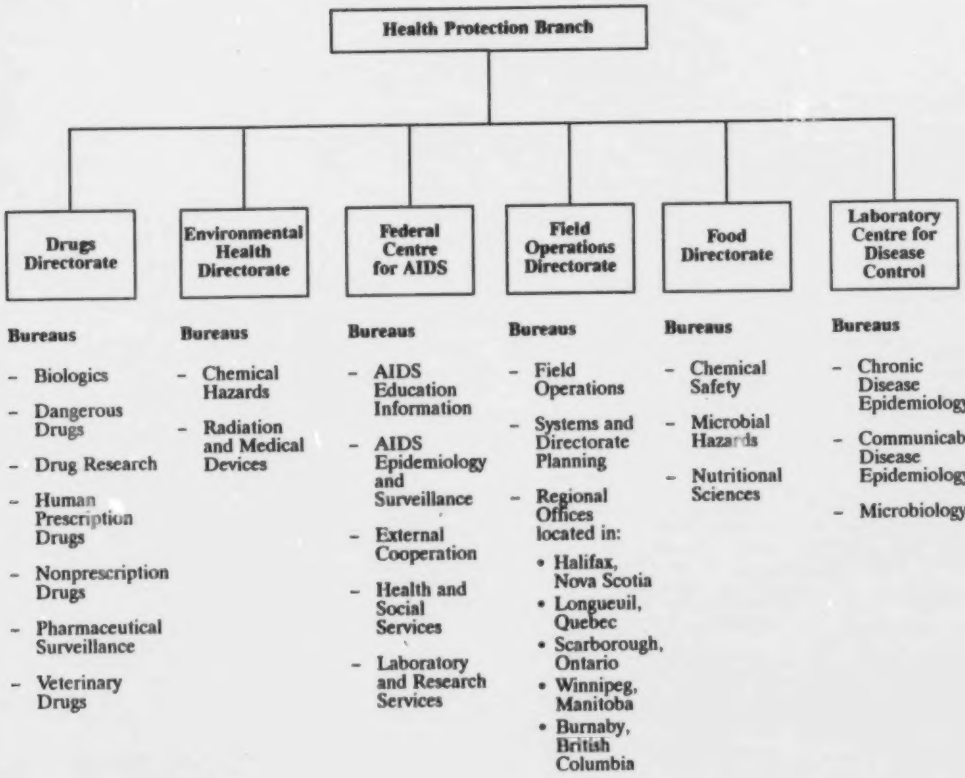


Figure 1: Organization of the Health Protection Branch

## Role of the Drugs Directorate

In general, the Drugs Directorate is responsible for supervising the availability and use of drugs before they are marketed. The Drugs Directorate, as shown in Figure 1, is composed of seven bureaus:

- Bureau of Biologics
- Bureau of Dangerous Drugs
- Bureau of Drug Research
- Bureau of Human Prescription Drugs
- Bureau of Nonprescription Drugs
- Bureau of Pharmaceutical Surveillance
- Bureau of Veterinary Drugs

**Bureau of Biologics**

The Bureau of Biologics is responsible for all regulatory activities that involve biologic drugs. These activities include:

- the evaluation of new drug submissions,
- procedures for lot release,
- inspections of biologic-drug-manufacturing plants, and
- authorization of emergency drug sales.

**Bureau of Dangerous Drugs**

The Bureau of Dangerous Drugs administers legislation and performs regulatory activities related to controlled drugs, restricted drugs, and narcotics. These activities include:

- licensing,
- research authorization,
- monitoring of distribution and use, and
- control of seized drugs and other assets.

**Bureau of Drug Research**

The Bureau of Drug Research is responsible for providing scientific expertise and information to other bureaus in the Drugs Directorate and to the Field Operations Directorate. Its activities include:

- scientific evaluation,
- computer support,
- statistical and epidemiological support, and
- laboratory research and testing.

**Bureau of Human Prescription Drugs**

The Bureau of Human Prescription Drugs is responsible for drugs destined for human use that are available to consumers only on prescription. The bureau's activities include:

- evaluating drug submissions,
- authorizing emergency drug sales,
- health hazard evaluations for potential recalls, and
- evaluating Drug Identification Number (DIN) applications.

**Bureau of Nonprescription Drugs**

The Bureau of Nonprescription Drugs is responsible for the regulation of drugs for human use that a consumer may obtain without a prescription, and for all cosmetics and disinfectants. The bureau's activities include:

- evaluating drug submissions,
- determining health hazards, and
- conducting reviews of advertising for drugs and cosmetics.

**Bureau of Pharmaceutical Surveillance**

The Bureau of Pharmaceutical Surveillance is responsible for activities related to all drugs. This includes:

- evaluating drug submissions for generic drugs,
- administering and interpreting regulations for good manufacturing practices,
- issuing DINs,
- conducting pharmaceutical market research, and
- co-ordinating the distribution of drug submissions and adverse drug reaction reports.

**Bureau of Veterinary Drugs**

The Bureau of Veterinary Drugs performs activities related to the regulation of drugs used to treat animals.

## Role of the Field Operations Directorate

The Field Operations Directorate is responsible for surveillance of drug manufacturers and of drug products once they are on the market. The Directorate's activities related to drugs include:

- inspection of pharmaceutical manufacturers, importers, and distributors,
- analysis of marketed products to verify compliance with applicable standards,
- customs surveillance to prevent importation of unacceptable products,
- co-ordination of recalls of violative products,
- investigations of consumer, professional, or trade complaints,
- prosecutions,
- management of health hazard crises,
- analysis for polices forces of illicit drugs, and
- inspection of pharmacies to verify compliance with regulations related to the sale of narcotic and controlled substances.

The Field Operations directorate is also involved in activities related to foods, cosmetics, medical devices, and tobacco products.

Program policy, planning, and co-ordination is carried out in the National Capital Region and implemented at Directorate offices and laboratories across Canada.

## Other HPB Directorates

Other directorates within the HPB share the duty of protecting public health.

- The Environmental Health Directorate deals with the integrity of the human environment. This mandate includes regulating the sale of tobacco products, the use of various medical devices, and exposure to radiological hazards.
- The Food Directorate is responsible for ensuring the safety and nutritional quality of food.
- The Laboratory Centre for Disease Control provides epidemiological services, laboratory surveillance, and diagnostic procedures for chronic and communicable diseases, and promotes investigation into health problems.
- The Federal Centre for AIDS works toward controlling the spread of HIV infection in Canada and assisting individuals who have contracted the virus.

While most drug-related programs are conducted by the Drugs Directorate and the Field Operations Directorate, other HPB directorates play significant roles in certain areas. For instance, an authorization by the Drugs Directorate for the emergency sale of a drug for treating a victim of HIV infection might involve the Federal Centre for AIDS. The Poison Control Program is administered by the Laboratory Centre for Disease Control. The Environmental Health Directorate is responsible for the regulation of radiopharmaceuticals.

## The Regulatory Process

Requests for changes to the *Food and Drugs Act* and the *Narcotic Control Act* come from many sources: the government, professional or trade organizations, consumer groups, industry, and police forces. When identifying a need for new or changed regulations, the Health Protection Branch considers such matters as health hazards, fraud, surveillance problems, and international obligations and standards. Major policy initiatives and proposals for regulatory amendments are communicated to the drug industry, health professionals, and consumers in Information Letters distributed by the HPB or through the Canada Gazette and the Federal Regulatory Plan. Comments submitted by concerned parties are considered in the drafting of regulatory amendments.

Proposed regulations and their associated Regulatory Impact Analysis Statement are reviewed by the Minister of National Health and Welfare and, if the Minister agrees, are presented to the Governor-in-Council (a committee of the Cabinet) for pre-publication in the Canada Gazette, Part I. When passed, the new regulations appear in the Canada Gazette, Part II, which is published twice monthly and which contains all new and amended federal regulations.

## Use of Expert Advisory Committees

The assistance of individuals who possess expert knowledge and judgment in specific technical, scientific, or medical fields is required by the HPB from time to time to augment the expertise of its staff. When it is determined that such a committee should be established, the HPB may publish an Information Letter stating the terms of reference for the committee. Committee members are selected by the HPB after an evaluation of the nominees.

## Guidelines

To assist drug manufacturers in complying with drug regulations, the Drugs Directorate publishes guidelines for the industry. Published or soon-to-be-published guidelines are identified in "Other Publications for Reference" at the back of this booklet.

# 3. Drugs and Their Availability

The availability of drugs is governed by considerations of safety and effectiveness, including the potential for misuse and the amount of professional consultation required. At one end of the spectrum are drugs that may be bought in a grocery store by any person, for example, calamine lotion; at the other end are drugs that may be legally obtained only by a research institution that has received an authorization from the Minister of National Health and Welfare, for example, LSD (lysergic acid diethylamide). The former can provide relief from an easily self-diagnosed minor irritation; the latter has no known medicinal use but has powerful, hazardous effects.

Health professionals (dentists, nurses, pharmacists, physicians, and veterinarians) play important roles in determining the availability of drugs to the public. The extent of professional involvement depends on considerations of safety. Many of the rules concerning drug availability are rooted in federal laws, but the distribution of certain drugs may be further restricted by provincial pharmacy laws. It is important to note that provincial laws govern the practice of all health professions.

## Vaccines, Serums, Radiopharmaceuticals, Antitoxins

Vaccines, serums, radiopharmaceuticals, and antitoxins are administered by qualified medical personnel. Normally, a patient has access to these drugs only through a physician.

## Nonprescription Drugs

As the term *nonprescription* suggests, these drugs may be obtained without a medical prescription. The actual place of sale is regulated by provincial law, usually in an act relating to the practice of pharmacy.

While it is not possible to definitively categorize nonprescription drugs, these drugs generally fall into three groups:

- proprietary medicines (GPs),
- over-the-counter drugs (OTCs), and
- drugs to be used in consultation with a physician.

Proprietary medicines (or GPs, as they are sometimes called) are products that may be purchased in any retail outlet. Proprietary medicines are identified on their labels by the letters GP (for "General Public"), followed by an eight-digit number. Proprietary medicines are intended for treating the symptoms of minor self-limiting illnesses that do not require the advice or intervention of a health professional. Examples of GPs are some medicated shampoos, cough drops, and fluoride toothpastes.

OTCs are identified on their labels by the letters DIN (for "Drug Identification Number") followed by an eight-digit number. For the most part, although a prescription is not required, over-the-counter drugs are available only in pharmacies. Like GPs, OTCs are intended to relieve the symptoms of minor self-limiting illnesses. However, it is recommended that, for certain members of this group, the advice of a health professional be obtained concerning use. Examples of OTCs are some laxatives, cough and cold remedies, sinus and nasal preparations, and many vitamins. Disinfectants are also included in this group.

The third and smallest group is composed of drugs that should be used only after consultation with, and recommendation by, a physician. These drugs are occasionally intended for long-term use and include medicines such as insulin, nitroglycerin, muscle relaxants, and antispasmodics.

**Drug or Cosmetic?**

The public may perceive certain products to be cosmetics, when, because the products alter bodily functions, they are, by definition, drugs, and are regulated as such. Under drug regulations, these products are considered to be nonprescription drugs. For example:

- A toothpaste is a cosmetic when it cleans, whitens, and brightens teeth; it is a drug when an ingredient, such as fluoride, is added to help prevent tooth decay.
- A deodorant is a cosmetic because it masks odor resulting from perspiration; an antiperspirant is a drug because it suppresses the flow of perspiration.

### Federal Law or Provincial Law?

Provincial law may be more restrictive (but not less restrictive) than federal law. For instance, some drugs are nonprescription drugs at the federal level but prescription drugs at the provincial level. For example:

- British Columbia: ephedrine and its salts (for internal use, and containing ephedrine as the single active ingredient).
- Ontario: lidocaine and its salts (for ophthalmic or parenteral use).

All prescription drugs, however, have the same status provincially as they do federally.

## Prescription Drugs

Many drugs are available to the public only after consultation with a medical practitioner (i.e., dentist, physician, or veterinarian) and presentation of a prescription to a pharmacist. A prescription is an order, given by a medical practitioner, that states the amount of a particular drug to be dispensed for the person named in the order.

The main reasons for requiring additional control of prescription drugs are the need for professional direction and supervision in their use and, in some cases, the need to minimize the potential for misuse or abuse.

Prescription drugs are categorized according to the extent of control necessary for their safe use. The categories are:

- vitamins A, D, K, and folic acid,
- Schedule F drugs,
- controlled drugs, and
- narcotic drugs.

### Vitamins A, D, K, and Folic Acid

Although usually sold as nonprescription drugs, preparations of vitamins A and D for humans require a prescription when the maximum daily dose recommended on the label exceeds 10 000 IU and 1 000 IU, respectively. Large doses of these vitamins can be toxic. Prescriptions are also required for folic acid when the recommended daily dose is greater than 1 mg and for all preparations of vitamin K.

**Schedule F Drugs:** Pr

Approximately 600 drug substances are listed in Schedule F to the *Food and Drug Regulations*. These substances are as varied as antibiotics, hormones, and tranquilizers. Schedule F, perhaps more than any other schedule, is subject to frequent changes. Additions or deletions from Schedule F result from:

- the introduction into the marketplace of new drug substances;
- newly acquired knowledge regarding hazards associated with certain substances;
- the determination that certain prescription drugs are safe enough to be reclassified as nonprescription drugs; and
- knowledge of changing patterns of misuse and abuse.

The symbol Pr must appear on the labels of these drugs.

Schedule F is divided into Part I and Part II. Part I lists most of the drugs covered by Schedule F (both human and veterinary). Part II lists drugs that can be obtained *without* a prescription if they are destined for veterinary use.

**Controlled Drugs:** ◇C◇

At present, about 14 primary drugs and their derivatives are classified as controlled drugs and are listed in Schedule G to the *Food and Drugs Act*. These drugs are stimulants (e.g., amphetamines, methamphetamines) and sedatives (e.g., barbituric acid, methaqualone).

The symbol ◇C◇ must appear on labels and all professional advertisements for these drugs.

As a result of misuse, five of the stimulants and all of their derivatives are classified as *designated drugs*. These drugs may be prescribed only for the following conditions:

- in humans: narcolepsy, hyperkinetic disorders in children, mental retardation (minimal brain dysfunction), epilepsy, parkinsonism, and hypotensive states associated with anesthesia;
- in animals: depression of cardiac and respiratory centres.

**Narcotic Drugs: "N"**

Narcotic drugs, controlled by the *Narcotic Control Act* and *Regulations*, are listed in the Schedule to that Act. Examples of drugs in this group are cocaine, opium, codeine, morphine, phencyclidine, and *Cannabis* (marijuana).

Some narcotic drugs have a legitimate medicinal use, such as the relief of pain. However, their psychotropic effects (ability to modify mental activity) and addictive properties have led to stringent restrictions on their availability. In addition, the letter "N" must appear on all labels and professional advertisements for these drugs.

Codeine, for example, has common medicinal uses. However, Section 36 (1) of the *Narcotic Control Regulations* states that the only preparations that a pharmacist may sell to the public without a prescription are:

- oral preparations containing not more than 8 mg, or its equivalent, per tablet or other dosage unit of codeine phosphate, or
- liquid preparations with not more than 20 mg, or its equivalent, of codeine phosphate per 30 mL.

Such products must also contain at least two additional medicinal ingredients (e.g., ASA, pheniramine maleate) and should not be administered to children except on the advice of a dentist or physician.

**Prescription Records**

When a pharmacist fills a prescription for a scheduled drug, a record of the prescription must be retained by the pharmacist for a minimum of two years. If a pharmacist receives a verbal prescription, it must be recorded in writing and the pharmacist must be satisfied that the source of the verbal order is legitimate.

Prescriptions for scheduled drugs must include the following information:

- date and number of the prescription;
- name and address of the person for whom the prescription is written;
- name and quantity of the drug specified by the medical practitioner;
- name of the person dispensing the prescription and name of the practitioner who prescribed it; and
- directions for use given with the prescription, including the number of times, if any, it can be refilled.

Refills are permitted only when authorized by a medical practitioner. Each time a prescription is refilled, the following information must be recorded on the original prescription or in a suitable patient record system:

- quantity of the drug dispensed,
- date of refill, and
- name of the person dispensing the prescription.

A narcotic prescription may not be refilled; a new and separate prescription from a practitioner is required. However, partial filling of prescriptions is permitted if the total quantity eventually dispensed does not exceed what was originally authorized.

Every other month, pharmacists are required to report prescription sales for specific narcotic and controlled drugs.

## Restricted Drugs

Restricted drugs, most of which have hallucinogenic properties (they alter perception of objective reality with serious physiological and psychological effects), have no recognized medicinal use and are dangerous. There are about 38 such chemicals listed in Schedule H to the *Food and Drugs Act*. The most well-known is lysergic acid diethylamide (LSD). Restricted drugs are available only to institutions involved in highly specialized research. An authorization from the Minister of National Health and Welfare is required before such a drug may be sold.

## Veterinary Drugs

Drugs listed in Part I of Schedule F to the *Food and Drug Regulations* may be sold only on prescription, whether for human or for veterinary use. A prescription is not required for any drug listed in Part II provided that the drug is in a form unsuitable for human use or specifically labelled "for veterinary use only."

### Drug Residues in Food

Drug residues in foods of animal origin can cause serious health consequences, in terms of toxicity and allergic responses, in individuals that are sensitive to such effects. To minimize this risk, the labels of veterinary drugs used to treat food-producing animals must specify a *withdrawal period* (also called the *withholding period*).

The withdrawal period is the time that must elapse between the last administration of a drug and the use of the animal as food or as a source of food. The withdrawal period ensures that no harmful residues remain in edible products. Depending on the type of food-producing animal, the rule is applied in two ways.

- For animals that are used as sources of meat products, the withdrawal period is the time between the last use of the drug and the time when the animal is slaughtered.

- For animals that are used to produce a food product (e.g., milk, eggs, honey), the withdrawal period is a measured period following the last use of the drug during which products obtained from the animal (if any) must not be used.

Antibiotics that leave residue in the milk of lactating cows longer than 96 hours after administration must not be used.

The regulations to the *Food and Drugs Act* include *maximum residue limits* for approximately 37 drugs. These limits specify the concentration above which a drug residue in a certain food (e.g., milk, eggs, chicken) would be unacceptable.

**Medicated Animal Feeds**

The regulation of medicated animal feeds is shared by the Health Protection Branch and Agriculture Canada. Information on the use of medicated animal feeds is contained in Agriculture Canada's *Compendium of Medicating Ingredients* brochures, which specify drugs, dosages, indications, and conditions of use applicable to the manufacture and sale of registered medicated feeds. Only drugs that comply with the *Food and Drugs Act* and that are listed in the *Compendium* are eligible for registration by Agriculture Canada.

# 4. New Drugs

A *new* drug is any drug that has not been sold in Canada for sufficient time, and in sufficient quantity, to establish its safety and effectiveness under use or its recommended conditions for use.

## Research

It has been estimated that to arrive at one new, marketable drug, chemists create or isolate up to 5000 chemical substances. After a chemical substance has been isolated and purified, the new compound is administered to tissue cultures, or a variety of small animals, or both, to see whether there are significant physiological or behavioural changes (in whole animals) or morphological or biochemical changes (in bodily organs). The results indicate whether the drug is pharmacologically active and may be useful in reversing the pathophysiology of disease states in humans or animals. If promising results are obtained from this initial study, a variety of animal and *in vitro* tests are completed, including mutagenicity, carcinogenicity, and reproductive studies as well as studies of effects on the immune system.

## Preclinical Testing

Initially, tests are conducted on non-diseased animals of at least two mammalian species (one must be a non-rodent) to determine the dose range—from non-toxic to lethal—of the compound. If a substance seems to possess potentially valuable pharmacological activity, as well as toxicity values considered to be acceptable, the manufacturer may then apply to the HPB for permission to conduct a clinical trial under a responsible clinical investigator.

## Clinical Trials

Extensive clinical testing is used to determine a new drug's tolerated dose, effectiveness, and safety in humans (or animals, in the case of veterinary drugs). To determine the compound's kinetics and the level of tolerance, and the prevalence of adverse effects, the compound is administered to healthy volunteers, gradually building to the predicted effective dose. At the same time, the manufacturer assesses the requirements for large-scale production of the compound.

To be able to perform clinical trials, the manufacturer of a new drug must file an Investigational New Drug Submission with the Drugs Directorate. This submission requests permission to distribute the drug to responsible clinical investigators that are named in the submission.

The information that is offered in an Investigational New Drug Submission must include all data pertaining to testing on humans and animals that has been performed up to the time of the submission. For a veterinary drug, data must be available to establish that the administration of the drug as recommended will not result in harmful drug residues in food products that are obtained from animals treated with the new drug.

Because the method of manufacture may affect the efficacy and safety of a drug, information on the manufacturing methods, standards used in manufacturing, and stability of the drug substance and its dosage form must be presented in the submission. This information ensures that the product that is eventually sold to the public has the composition that was determined to be effective and safe in the clinical trials.

The investigator is subject to comprehensive regulations because clinical trials are carried out on persons or animals that exhibit the disease state or condition that the compound is expected to treat; the results of a clinical trial usually compare the tested compound with other drugs or older methods of treatment used for the same disease or condition. In many studies, a placebo is included to validate the test system. If clinical studies prove that the compound has potential therapeutic value that outweighs the risks associated with its use (e.g., adverse effects, toxicity), the manufacturer may then file a New Drug Submission.

## New Drug Submissions

Before marketing a new drug, a manufacturer must file a New Drug Submission with the Drugs Directorate. A New Drug Submission contains virtually all information known about the drug, and the results of preclinical and clinical studies at several dose

strengths in the dosage forms that are to be marketed. The submission is reviewed to ensure that all necessary conditions are met before the drug is marketed.

Information about the drug includes:

- the drug's proper name and chemical name(s),
- details of the method of manufacture and purification, and
- the drug's physicochemical, biological, pharmacological, pharmacodynamic, pharmacokinetic, teratologic, and toxicologic properties.

Information about the dosage form includes:

- a quantitative listing of all ingredients used in the formulation,
- the method used to manufacture the dosage form,
- quality control information,
- packaging and labelling details,
- results of stability tests,
- therapeutic claims,
- side effects, and
- details of clinical studies to support the safety and efficacy of the drug.

Submissions can range in size from a few pages to several hundred volumes. Samples of the market-ready form of the new drug may also be included with the submission for possible analytical testing.

Drug Submission Application forms may be obtained from the Submission and Notification Administration Division of the Bureau of Pharmaceutical Surveillance.

**Review of the Submission**

New Drug Submissions are critically reviewed by multidisciplinary teams in the Drugs Directorate. A first review of a New Drug Submission may, on occasion, be undertaken by an external expert under contract to the HPB. A final review deals with the wording of the product monograph, which provides complete information about the drug, as well as complete prescribing instructions for physicians. When these aspects of the New Drug Submission are found to be satisfactory, the labels are examined, a Drug Identification Number (DIN) is assigned, and a Notice of Compliance is issued. It is the Notice of Compliance that permits the manufacturer to sell the product. If a Notice of Non-Compliance is issued, the manufacturer has failed to meet all of the requirements. The manufacturer may appeal the decision with the Drugs Directorate.

## Biocomparable Drugs

The Bureau of Pharmaceutical Surveillance evaluates new drug submissions for biocomparable pharmaceuticals that would normally be available on prescription. The safety and efficacy of biocomparable products are determined through comparative bioavailability studies in healthy volunteers instead of clinical trials in patients. Biocomparable products may include both generic drugs and new formulations of drugs from the original manufacturer. The evaluation process includes assessments of product chemistry, effectiveness and safety, manufacturing specifications, labelling, and monographs.

## PER Scheme

In June 1979, the members of the European Free Trade Association implemented the Scheme for the Mutual Recognition of Evaluation Reports on Pharmaceutical Products (PER Scheme). Canada became a member of the PER Scheme in February 1990. At present, Australia, Austria, Canada, the Federal Republic of Germany, Finland, Hungary, Italy, the Netherlands, Norway, Sweden, Switzerland, and the United Kingdom are participants.

Once a pharmaceutical product has obtained registration (marketing licence) in a PER Scheme country, another participating country may request an evaluation report on the product from the country that registered it. Such a report contains an evaluation of the scientific data and documentation submitted by the manufacturer for the registration of the product. The authority requesting the report may accept all or part of the evaluation already carried out but has no obligation to do so.

## Radiopharmaceuticals

Owing to the unique nature of radiopharmaceuticals and kits for their preparation, review of Investigational, New Drug, and drug status submissions for these drugs are the responsibility of the Bureau of Radiation and Medical Devices, Environmental Health Directorate.

## Marketing Controls

Once a new drug is on the market, controls do not cease. A drug may retain its new drug status for a number of years. Only when the Drugs Directorate is confident that sufficient information on safety and efficacy has been accumulated from the drug's general use will the drug be released from the stringent controls that are applied to all new drugs. The manufacturer must report any new information received concerning serious side effects, including failure on the part of the drug to produce the desired effect. The manufacturer is also required to notify the Drugs Directorate about any animal tests that have provided new safety information. A Notice of Compliance for a new drug can be suspended and the drug removed from the market to protect public health. Even drugs that are not classified as new drugs (e.g., conjugated estrogens) are scrutinized for the purpose of re-defining their role in therapy.

## Emergency Drugs

Under certain circumstances, the Drugs Directorate may authorize the sale, in Canada, of drugs that are currently marketed in other countries but have not yet received clearance for clinical trials or marketing in Canada. These emergency drugs are sold to specific medical practitioners for specific patients when a medical emergency exists and standard therapy is ineffective in treating the condition.

If an emergency drug is requested by a physician or a pharmacist on behalf of a physician, the following information must be provided:

- the name of the physician administering the drug,
- the drug name and supplier,
- the quantity and dosage form needed,
- the age and sex of the patient,
- the diagnosed condition, and
- the reason or condition for the drug request.

All serious adverse reactions to drugs obtained through the Emergency Drug Release program are to be reported to the Drugs Directorate.

# 5. Drug Standards

## What is a Drug Standard?

A drug standard is a set of measurable characteristics or specifications that define and identify a particular drug. A standard ensures uniform drug quality among different products and may be concerned with:

- physical and chemical drug descriptions,
- drug identification procedures,
- permitted pH ranges,
- tests for heavy metals,
- pyrogen and sterility requirements,
- assay methods,
- potency limits,
- release characteristics (e.g., dissolution),
- packaging and storage requirements, and
- special label instructions for consumers.

### Single-Ingredient Drugs

There is no single set of standards used by international drug manufacturers. However, most drug substances and single-ingredient formulations are manufactured to the standards contained in the following publications (known as Schedule B publications):

- *Pharmacopée Française* (Ph.F.)
- *Pharmacopoeia Internationalis* (Ph.I.)
- *The Canadian Formulary* (C.F.)
- *The British Pharmacopoeia* (B.P.)
- *The British Pharmaceutical Codex* (B.P.C.)
- *The National Formulary* (N.F.)
- *The United States Pharmacopeia* (U.S.P.)

The drugs listed in these publications, or in the Regulations, are known as *official drugs*. For certain drugs, specific requirements are set out in the Regulations.

A manufacturer may use its own standard, known as a "Manufacturer's Standard" or "house" standard, in the production of drugs listed in the Schedule B publications. The house standard, however, must meet the most stringent criteria for purity and potency set out by the Schedule B publications.

**Multiple-Ingredient Drugs**

For most multiple-ingredient drugs and new single-ingredient drugs, there are no standards described in the Regulations or in the Schedule B publications. In these cases a "professed" standard—developed by the manufacturer and approved by the HPB—is used.

## Some Legislated Drug Specifications

A few examples of drug specifications legislated in the *Food and Drug Regulations* follow:

- Compressed tablets that will be swallowed whole (except for enteric-coated tablets) must, under specified test conditions, disintegrate within 45 minutes if coated, and within 60 minutes if uncoated. This specification ensures that the tablets do not pass through the digestive system whole.
- Enteric-coated tablets must not, under specified test conditions, disintegrate when placed in an acidic medium for 60 minutes. They must, however, disintegrate within 60 minutes after being removed from the acidic medium and placed in an alkaline medium. This specification ensures that the tablets pass through the acidic environment of the stomach and disintegrate in the alkaline environment of the upper small intestine.
- Safety factors such as sterility, particle sizes below specified limits, and the absence of pyrogens must be maintained in parenteral drugs and in drugs destined for use in the human eye.
- Certain drugs must meet Canadian standards specified in Division 6 of the *Food and Drug Regulations* (e.g., estrogens, digoxin).

# 6. Good Manufacturing Practices

All phases in the production of drugs for sale in Canada require meticulous care. Therefore, legislation establishes the minimum acceptable conditions under which drugs should be produced. The conditions relate to:

- personnel involved in drug production;
- the premises in which drug production takes place, the equipment used, and the sanitation program that is followed;
- the raw materials used in drug production;
- manufacturing controls and quality control;
- testing of packaging and the finished product;
- record-keeping and drug samples;
- stability of drug products; and
- sterility of drug products.

## Personnel

People are the most important element of any pharmaceutical operation. Each person should have the right attitude and the proper training to do the job. Personnel in the manufacturing and quality control departments should be supervised by persons who have university or equivalent degrees related to the work being carried out and who have had practical experience in their area of responsibility.

## Premises

The premises in which drug production takes place should possess features that allow manufacturing to be clean, orderly, and free of contamination. These features include:

- suitable environmental conditions,
- allowances for adequate cleaning and sanitation, and
- a design that minimizes the possible contamination of a drug during its production.

## Equipment

Poor maintenance or misuse of equipment, and the presence of foreign matter must be eliminated to prevent the contamination of a drug during production.

## Sanitation

A plant must establish a comprehensive sanitation program to ensure that a high level of cleanliness is maintained when drugs are produced. Employees should always:

- be dressed in suitable clothing,
- follow good hygienic practices, and
- be aware of the need to avoid working in a drug production area if they are carriers of a communicable disease or have exposed lesions.

## Raw Materials

Substances that are used in the production of a drug product must always be tested against an acceptable standard before use. Substances that are likely to experience a change in composition during storage should be retested if held in storage for more than two years after the original analytical tests.

## Manufacturing Control

To ensure the purity of the drug product, controls must be exercised at every stage of production, from the moment raw materials enter the plant, until the time the product is released for sale. These controls are the foundation upon which the quality of the drug product rests.

When a drug is produced outside the manufacturer's direct control, the manufacturer must ensure that all suppliers meet the same high standards. Should these controls fail, the manufacturer must be able to effectively and rapidly recall the defective drug.

## Quality Control

All steps in the production of a drug must be independently approved and audited by professional personnel in a manufacturer's quality control department. This group must ensure that all components of the drug product are tested and approved before they are used and that the final drug product is tested before sale.

The combination of manufacturing and quality controls is often called *quality assurance*.

## Packaging Material Testing

All labels and all materials that come into contact with the drug product must either be tested or examined before being used.

## Final Product Testing

The controls exercised during production are complemented by *in vitro* testing of each batch of a drug product before it is released for sale. Aspects that are tested include:

- drug identity,
- purity of the drug,
- potency of the drug,
- disintegration or dissolution (of tablets and capsules), and
- other specifications for the drug.

In the case of drugs for parenteral use, process validation is also a means to ensure the sterility of the drug in its final container.

## Records

A record of all procedures and tests must be kept by the manufacturer so that a complete history of the production of each lot or batch of a drug product is available for review. These records must be retained for a period of time that exceeds the time that the drug product is sold.

## Samples

The manufacturer must retain, for a specified period of time, a sample of each batch of drug produced.

## Stability

For each drug sold, the manufacturer must determine how long potency is retained. In specific instances, an expiry date must be added to the label.

## Sterile Products

Drug products that must be sterile when used must be produced with additional precautions and controls to ensure that they do not become contaminated.

# 7. Drug Safety and Quality

## The Drug Identification Number (DIN/GP)

All drugs must be evaluated by the Health Protection Branch before they may be sold. In addition, to facilitate its monitoring programs, the Health Protection Branch must be able to quickly identify all marketed drugs. As a result, a manufacturer or importer must apply for, and obtain, an eight-digit drug identification number from the HPB before selling a drug. The information provided in these applications enables the HPB to maintain files on every drug product on the market. These files include:

- the name of the drug,
- names and addresses of all persons or firms whose names appear on the drug label,
- the use or purpose for which the drug is recommended,
- a quantitative list of medicinal ingredients (i.e., active ingredients),
- copies of all labelling,
- the dosage form sold (i.e., capsule, powder, liquid, etc.),
- the recommended dosage,
- the recommended route of administration, and
- a quantitative list of colouring agents.

Six characteristics are used to generate the eight-digit drug identification number:

- the manufacturer,
- the active ingredient(s),
- the strength of the active ingredient(s),
- the route(s) of administration,
- the dosage form, and
- the name of the drug.

If a manufacturer has two or more products that are identical in the six characteristics used to generate the number, but differ in brand name or in non-medicinal ingredients (e.g., colour), each product is assigned its own drug identification number. There are more than 17 000 drug products on record as being sold in Canada.

In the case of proprietary medicines, the eight-digit number is prefixed by the letters "GP" (General Public). All other drugs have the prefix "DIN" (Drug Identification Number).

**Who Uses the DIN/GP?**

The HPB uses the information in DIN/GP applications for planning and in emergency situations that require rapid identification of a product. Other groups that use the DIN/GP for various purposes include:

- provincial governments,
- health insurance companies,
- associations of health professionals,
- poison control information and treatment centres,
- hospitals and universities,
- drug manufacturers, and
- pharmacies.

Because the distribution of radiopharmaceuticals is more closely controlled than that of normal drugs, radiopharmaceuticals are exempt from DIN/GP requirements.

## The Inspection of Drug Production Facilities

Under the *Food and Drugs Act*, inspectors from the HPB's Field Operations Directorate have the authority to enter and inspect drug manufacturing and storage locations to monitor compliance with the *Act* and *Regulations*. Advice and guidance in interpreting the legislation are offered to manufacturers and distributors as needed. Inspectors are trained professionals, whose qualifications are similar to those of persons in charge of quality control in the facility.

When inspecting a facility, the inspector observes all production procedures, from receipt of components for drug production, to preparation of a form ready for distribution. The inspector may take samples of products for later examination.

Inspectors have the power to seize products that are in violation of, or are suspected to be in violation of, the legislation. A seizure may be made at the manufacturing, distributing, or retail level, and may occur for various reasons (e.g., failure of the drug to meet its standard, lack of sterility, labelling infractions, unsanitary storage conditions).

Following an inspection, which usually takes several days, the inspector meets with the manufacturer to discuss the findings and to indicate any deficiencies that require immediate attention.

As most drug manufacturers and distributors comply with the legislation, the HPB's basic philosophy in this regard is one of "voluntary compliance." As a result, when a violation occurs, and the matter is not serious, the manufacturer or distributor may be given the opportunity to correct the defect with periodic monitoring by the HPB's field inspectors. This is often the only action required.

However, when a violation is serious, or when repeated violations that are less serious come to the attention of the HPB, the violator may be prosecuted.

## Analytical Programs

Two regional offices of the HPB have drug laboratories with fully qualified staffs that include chemists, microbiologists, and technologists. A drug's identity, potency, content uniformity, purity, sterility, dissolution rate, and disintegration time can be determined in these facilities and a regular program of product assessment is maintained.

Specialized facilities for national monitoring are located in the Ontario and Quebec regional laboratories. These units, called the Drug Quality Monitoring Laboratories, are equipped for automated determination of potency and content uniformity of drugs. The Drug Analytical Service (DAS) is an identification and quantitative analysis service that supports the efforts of police forces to control the illegal use of controlled, narcotic, and restricted drugs.

### Which Drugs Are Analysed?

The following types of drugs are analysed by HPB's testing facilities:

- drugs obtained as part of ongoing national monitoring surveys that help to assess the quality of drug products in the Canadian marketplace;
- drugs (usually controlled, narcotic, or restricted drugs) obtained from illicit channels and submitted by law enforcement agencies for identification (DAS);
- drugs whose quality is questioned by external sources, such as the public or professional groups; and
- drugs obtained during an inspection, to ensure their compliance with the *Food and Drugs Act* and *Regulations*.

## Imported Drugs

About 18 percent of the drug products sold in Canada are imported. An importer must maintain comprehensive information showing that the imported drugs are manufactured to correct specifications and under conditions that meet Canadian requirements. In addition, the following conditions must be met:

- The name and address of the drug importer must appear on the drug label (excepting Schedule C and D drugs, for which the information must appear on the licence application).
- The premises where Schedule C and D drugs are manufactured must be inspected by Health Protection Branch inspectors and must be licensed before the drugs can be imported.

To monitor the technical and scientific competence of foreign pharmaceutical firms, and to provide for prompt communication of potential hazards, the Health Protection Branch exchanges information with agencies in other countries (e.g., the U.S. Food and Drug Administration).

Imported drugs may be detained or refused entry into Canada at the time of importation. If the product defect that caused the refusal cannot be corrected, the drugs are denied entry entirely; if the defect can be corrected, the importer may be permitted to receive the shipment on condition that a correction will be made within a specified period of time.

## Recalls

Drug manufacturers may receive information concerning product defects from a variety of sources, including the Health Protection Branch. As a result, a manufacturer may initiate, or may be requested to initiate, a product recall. Detailed information that relates to the defect and the distribution of the product (at the distributor or retail level) must be supplied to the HPB. The HPB uses this information, as well as information from other sources, to decide whether the product defect represents a serious health hazard and how extensive a recall is required (i.e., to wholesale, retail, or consumer level). If there is a serious threat to the safety of the consumer, a public alert is issued through the media.

In co-operation with provincial and municipal health agencies and industry associations, the HPB has established a National Emergency Recall Plan to deal with drugs that present serious and widespread health hazards to the public. For example, if a commonly-used nonprescription drug were to be contaminated with strychnine, the recall plan would enable the HPB to mobilize many people at different levels of government (federal, provincial, and municipal) to correct the

problem. A public alert would also be issued. So far, the recall plan has never been implemented; past drug recalls have not required such mobilization of resources.

## Drugs for Export

Canada participates in the World Health Organization's Certification Scheme for pharmaceutical products moving in international commerce. This program provides, to nations that import drugs from Canada, information about the quality of drugs manufactured in Canada.

## Drug Quality Assessment Program (QUAD)

The QUAD program was initiated in 1971 to provide pharmacists, physicians, dentists, and other health professionals and purchasing agencies with information about the quality of drugs on the Canadian market. This information is based on the inspection reports and the analyses performed in the regional laboratories.

In 1975, the QUAD program was reoriented to enable the provincial governments to use the information for their drug reimbursement programs more effectively.

The program encompasses nearly 5 000 products, representing more than 800 substances manufactured by about 200 firms. Approximately 450 of these products are analysed each year, and data on an additional 600 to 700 is assessed.

Information is now provided on a regular basis to provincial and territorial departments of health and hospital drug-purchasing groups.

## Complaints and Investigations

Investigations are conducted in response to complaints received from various sources outside the HPB. The primary sources are consumers, health professionals, and industry officials. The first step in an investigation usually determines how the product has been used and handled. If user error is eliminated as a possible cause of the complaint, the investigation proceeds to the manufacturer level and, where necessary, samples of the drug are analysed in the HPB's laboratories.

Product complaints should be directed to the nearest regional office of the Health Protection Branch.

# Postmarketing Pharmaceutical Surveillance Program

The Postmarketing Pharmaceutical Surveillance Program monitors drug products through:

- Adverse Drug Reaction (ADR) reporting,
- single assessment and evaluation, and
- drug use review.

### Adverse Drug Reaction Reporting

An ADR is any undesirable effect in a patient that is suspected of stemming from the use of a certain drug. ADR includes the failure of a drug product to produce its labelled pharmaceutical activity. Proof that a certain drug is the cause of the patient's condition is not a requirement for reporting the reaction; the suspicion that the condition is drug-related is all that is necessary.

ADR case reports are provided by health practitioners, on a voluntary basis, to Regional Reporting Centres. Reports are also sent directly to the National Reporting Centre by pharmaceutical manufacturers and are entered into a computerized database. The following types of adverse reactions must be reported to the HPB:

- unexpected adverse reactions—any undesirable effect that is not consistent with available product information or the information on the product's labels;
- serious adverse reactions—any undesirable effect that contributes significantly to disability or illness, including reactions that result in hospitalization or that require significant medical intervention; and
- adverse reactions to recently marketed drugs—any undesirable effect resulting from the use of a drug that has been commercially available for less than five years, regardless of the nature or severity of the effect.

The form used to report an ADR for human drugs, vaccines, cosmetics, or food products may be obtained from the Product Related Disease Division of the Bureau of Pharmaceutical Surveillance. The form used to report an ADR for veterinary drugs may be obtained from the Bureau of Veterinary Drugs.

### Assessment and Review

Adverse drug reaction reports are assessed for the seriousness of the reaction and for whether they may signal the need for further evaluation and action. Additional evaluation may be conducted by the

Canadian ADR Advisory Committee, whose recommendations stating the type of action considered necessary (e.g., modification of prescribing information, formal pharmacoepidemiology studies) are forwarded to the HPB.

A review of drug use patterns in terms of quantity and quality of use is integrated into the overall risk/benefit assessment of drug safety.

**Keeping the Program Current**

Canada's Postmarketing Pharmaceutical Surveillance Program is directly linked to the World Health Organization (WHO) Centre for International Drug Monitoring in Uppsala, Sweden. Canadian case reports are entered quarterly into the WHO database. Single assessments, alerts, and decisions regarding regulatory actions are communicated via a computerized network. This mechanism ensures that the program is kept abreast of drug safety topics that arise in more than 30 countries worldwide.

## Poison Control Program

When the Poison Control Program began in 1957, poison control centres were located in pediatric hospitals because, at the time, most poisoning cases involved children. Since then, however, the character of the poisoning problem has shifted, and the incidence of adults and adolescents being poisoned has increased. Approximately 100 000 reports are received annually. The types of drugs and drug combinations have changed. The increase in adult poisoning deaths is attributed to the use of multiple products (taking excessive amounts of more than one type of drug). Poisonings with tranquilizers among persons five years of age and older is also increasing. While the number of accidental poisonings seems to be levelling off, the number of intentional poisonings (i.e., suicide attempts) is increasing.

Today, more than 300 poison control centres are co-ordinated in a national network. The poison control centres are under the direction of the provincial departments of health, but the collection, co-ordination, and dissemination of information to the centres is handled by the Health Protection Branch.

The statistics on poisoning cases that are reported by the centres are entered into a computerized data base and appear annually in *Poison Control Program Statistics*, a publication of the Health Protection Branch. These statistics assist the HPB in determining which products need to be more carefully controlled through measures such as ingredient changes, child-resistant packaging, and improvements in labels and warnings.

The HPB has also published a booklet entitled *Emergency Treatment of Poisoning*, which is available to poison control centres and health professionals.

Most telephone directories list an emergency poison control centre number where health professionals and the public can report a poisoning and obtain immediate advice on possible antidotes and measures to alleviate detrimental effects.

# 8. Labelling, Packaging, and Advertising

Proper labelling, packaging, and advertising of drugs is stressed by Subsection 9(1) of the *Food and Drugs Act*:

"No person shall label, package, treat, process, sell or advertise any drug in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety."

## Labelling

The label of a drug product is one of the most important sources of drug information available to the consumer and the health professional.

In addition to the commonly understood meaning of "label," any literature that accompanies or belongs to a particular drug product is also considered to be labelling material. Two types of labels, inner and outer, accompany a drug product. An inner label is affixed to the product's immediate container; an outer label is located on the outside of a drug package.

The following information must appear on the label:

- the drug's proper name;
- the name and address of the drug's manufacturer or distributor (when applicable, the name and address of the Canadian agent or representative must be included);
- the lot number;
- a quantitative list of medicinal ingredients by their proper or common names;
- the DIN or GP number assigned to the drug (radiopharmaceuticals are exempt);
- the expiration date;
- the net contents of the container;
- directions for use; and
- the standard to which the drug was manufactured.

If the label has insufficient space to carry all the required information, some of it may be included on a package insert. The label should indicate that a package insert is included.

**Proper Name**

The proper name is assigned to the drug in the Schedule B publications or in the *Food and Drug Regulations*. The proper name usually differs from the chemical name (e.g., acetaminophen is the proper name for N-acetyl-p-aminophenol). If there is no proper name for the drug, its common name may be used.

**Lot Number**

The lot number is the means by which a drug can be traced in manufacture and identified in distribution. It is assigned by the manufacturer when the drug is produced.

**Expiration Date**

An expiration date must be included on the labels of certain products that do not maintain their potency, purity, and physical characteristics for at least three years from the date of manufacture.

**Net Contents**

The net contents is the net quantity of the drug in terms of weight, measure, or number. The indication of net contents should appear on the outer label. However, if there is no outer label, the information should appear on the inner label.

Note that when ASA is in a dosage form recommended only for children, the package must not contain more than 24 single doses.

**Directions for Use**

Adequate directions for the wise use of the drug must be included on the label. These include:

- the purpose of the drug,
- recommended dosage,
- route of administration,
- cautions and warnings, and
- contraindications.

To ensure safe and effective use of a drug, all labels must carry a recommended single or daily dose or dosage range. For some non-prescription drugs (known as limit-dose drugs), this dose is limited by legislation and may be exceeded only if the label states that a physician should be consulted; a reduced dosage must be stated when these drugs are recommended for children.

**Language of Labelling**

Directions for use can be in either French or English. However, directions for use must be in both French and English if the drug is available for sale without prescription in an open, self-selection area (such as an aisle in a pharmacy or corner store).

**Children and Label Precautions**

Compounds that contain codeine and that are sold without a prescription must carry a warning against administering the compound to children except on the advice of a physician.

Acetaminophen and ASA must carry warnings on the label that provide the following messages:

- The drug should not be administered to a child under two years of age, except on the advice of a physician. (Pediatric preparations of these drugs are exempt from this requirement.)
- The drug must be kept out of the reach of children.
- Packages containing more than two grams of ASA or acetaminophen contain enough drug to seriously harm a child.

The last two warnings must be preceded by a conspicuous symbol, such as a red octagon on a white background.

As a result of ASA's association with Reye's syndrome, a rare but serious illness, manufacturers of ASA have been asked to include a warning on the labels of non-prescription ASA products. The warning states that the drug should not be administered to, or used by, a child or a teenager before a physician or pharmacist has been consulted about Reye's syndrome.

Packages that contain more than 250 mg of iron must carry the following warnings:

- The package must be kept out of the reach of children.
- There is enough drug in the package to seriously harm a child.

These statements must be preceded by a conspicuous symbol, such as a red octagon on a white background.

Preparations that contain boric acid or sodium borate must caution against administration of the drug to children under the age of three years.

**Disposable Pressurized Containers**

The labels of disposable pressurized containers must call attention to the potential hazards inherent in the use of such containers. The statements "container may explode if heated" and "contents under pressure" must appear on the label. These cautions must be accompanied by precautionary statements regarding the handling of the container. The following symbol, accompanied by the word "Caution," must appear on the main panel of the label:

If the contents of the container are flammable, a statement indicating this fact must appear on the label together with an appropriate symbol designating the degree of flammability. For example:

### Radiopharmaceuticals

Special outer label requirements apply to radiopharmaceuticals. The label must include a licence number (see Chapter 9), a radiation warning symbol, and the statement "Caution—radioactive material." Licence numbers are also required on the outer labels of kits used in the preparation of radiopharmaceuticals.

### Storage Instructions

The storage instructions that may be included with a drug product are necessary to ensure that:

- the potency of the drug is maintained,
- the degradation of ingredients is prevented, and
- the user is protected from dangers inherent in the packaging, as in the case of aerosol containers.

Two examples would be the statements "Store at room temperature" and "Keep refrigerated."

### Vitamins and Minerals

Products that are used to treat certain disease states or deficiencies that require a high intake of certain vitamins and minerals are permitted to contain more than the maximum level specified in the vitamin and mineral regulations for most non-prescription drugs. Such products must be clearly labelled "For therapeutic use only" and should be used only on the advice of a physician.

Labels of all vitamin preparations must carry an expiry date.

### Veterinary Drugs

When drugs listed in Part II of Schedule F to the *Food and Drug Regulations* are sold without a prescription for use in animals, the label must contain the statement "For veterinary use only."

A withdrawal period must be included on the label of any veterinary drug that creates a residue when used in food-producing animals. This requirement, when met, ensures that proper use of the drug will leave no harmful residue in food derived from treated animals.

### Schedule A Diseases

Labels of drug products may not contain any claim about the drug's effectiveness in the treatment of Schedule A diseases, except where such a claim is necessary for the safe use of a parenteral (e.g., insulin) or a prescription drug.

### Labels of Drugs Sold by Prescription

Provincial legislation usually specifies the information that must appear on the label of a drug that is sold by prescription. Practitioners who prescribe and dispense the drug are expected to provide the necessary guidance and warnings to ensure that the drug is properly taken. This information may be communicated by the pharmacist and physician both orally and in written form.

### Label Monitoring

The Drugs Directorate maintains an ongoing monitoring program that assesses each manufacturer's compliance with labelling regulations.

## Packaging

Package requirements are determined by the various chemical and physical characteristics of drug products. Packages are designed to maintain the potency and purity of a drug for as long as possible. The package itself must not chemically interact with the drug.

Some examples of specialized drug packaging are:

- light-resistant containers for phenothiazine tranquilizers (light reduces their potency and shelf life),
- glass containers for nitroglycerin tablets (the potency of these tablets will diminish if stored in a semiporous plastic container),
- child-resistant packaging, and
- security packaging.

### Child-Resistant Packaging

In order to reduce the incidence of accidental drug ingestion by children, certain products require a child-resistant package (CRP). The products that require CRPs are those that contain:

- salicylic acid, its salts and salicylamide,
- ASA, its salts and derivatives,
- acetaminophen,

- liquid preparations containing more than five percent alkyl salicylates (e.g., oil of wintergreen), and
- preparations containing more than 250 mg of iron per package.

When these drugs are recommended only for children, they must be packaged in a CRP. When a drug is not solely recommended for children, at least one of the package sizes that are marketed must have a child-resistant package, and all other package sizes must carry a statement on the label indicating that the product is also available in a child-resistant package.

## Advertising

Professional advice is required for the proper diagnosis and treatment of certain diseases or conditions. As a result, professional advice is also required for the administration of certain classes of drugs. Therefore, advertising to the public is prohibited for:

- narcotics,
- controlled drugs,
- prescription drugs for human use (Part I of Schedule F to the *Food and Drug Regulations*),
- limit-dose drugs (non-prescription drugs that have recommended dosage limits) whose limits are exceeded,*
- drugs for treatment of Schedule A diseases,
- vitamins labelled "For therapeutic use only,"* and
- minerals labelled "For therapeutic use only."*

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* Except for name, price, and quantity.

The *Food and Drugs Act* stipulates that no food, drug, cosmetic, or device may be advertised as a treatment, prevention, or cure for any of the diseases, disorders, or abnormal physical states listed in Schedule A (reproduced in Figure 2).

| | |
|---|---|
| Alcoholism | Hypertension |
| Alopecia | Hypotension |
| Anxiety state | Impetigo |
| Appendicitis | Kidney disease |
| Arteriosclerosis | Leukemia |
| Arthritis | Liver disease |
| Asthma | Nausea and vomiting of pregnancy |
| Bladder disease | Obesity |
| Cancer | Pleurisy |
| Convulsions | Pneumonia |
| Depression | Poliomyelitis |
| Diabetes | Rheumatic fever |
| Disease of the prostate | Septicemia |
| Disorder of menstrual flow | Sexual impotence |
| Dysentery | Tetanus |
| Edematous state | Thrombotic and embolic disorders |
| Epilepsy | Thyroid disease |
| Gall bladder disease | Tuberculosis |
| Gangrene | Tumour |
| Glaucoma | Ulcer of the gastrointestinal tract |
| Gout | Vaginitis |
| Heart disease | Venereal disease |
| Hernia | |

Figure 2: Schedule A to the *Food and Drugs Act*

Controls on drug advertising ensure that advertising is directed at the proper audience, that false or misleading advertising is prevented, and that children are not the targets of drug advertising. Drug advertising is continuously monitored by the Health Protection Branch.

**Health Professionals and Drug Advertising**

The advertising restrictions listed above have been developed to protect the lay public and do not apply to advertising directed at health professionals. New developments in the field of medicine and treatments for Schedule A diseases are valuable to medical practitioners, and the information obtained through advertising aids in the assessment of the risk/benefit ratio of treatments.

**False, Misleading, or Deceptive Advertising**

The statement "... false, misleading or deceptive or is likely to create an erroneous impression ..." from Subsection 9(1) of the *Food and Drugs Act*, refers to advertising that:

- contradicts current medical or scientific knowledge,
- cannot be supported by clinically valid and statistically reliable data,
- contains confusing or misleading words and phrases, and
- gives an overall inaccurate impression.

Some terms that may be misleading when used in drug advertising are:

- **Natural**: Few drugs are so devoid of processing as to justify the description "natural."
- **Natural source**: Only drugs that are obtained by minimal processing (e.g., cod liver oil or drugs of a vegetable origin) may be described as "natural source."
- **Natural action**: This term should not be used, as all drugs act by artificially stimulating or assisting bodily functions.
- **Organic**: This term has no real meaning, as many drugs may be defined, chemically, as organic compounds.

Some promotional methods that are often unacceptable are:

- **Comparisons**: These are often incomplete, as they frequently highlight only the advantages of the advertised product and the disadvantages of the competitor's product; they often emphasize product differences that have little or no clinical significance.
- **Negative statements**: To say that a particular product is non-toxic implies that comparable products may be toxic.
- **Scientific or technical references**: The consuming public does not typically have the expertise to assess the validity of such references.

**Children and Drug Advertising**

Drug advertising should not be directed toward children, lest it encourage unsupervised use of drugs by children and establish drug-taking habits early in life. Therefore, the following kinds of drug advertisements are unacceptable:

- portrayals of children discussing drug products or requesting a certain drug,
- placement of more stress on a premium being offered than on the health reason for taking a drug,

- exaggeration of aspects of a product that would appeal to children (e.g., portraying drug-taking as fun or grown-up), and
- the promotion of drug products for children directly to children by using nationally known persons or characters (e.g., cartoon characters).

**Preclearance of Advertising**

As required by broadcasting regulations administered by the Canadian Radio, Television, and Telecommunications Commission, all drug advertisements presented on radio and television must be precleared by the Drugs Directorate.

Advertisements that are directed to the general public and that appear in newspapers, magazines, and direct mail pieces are not subject to preclearance. They are, however, continuously monitored and are subject to the same types of legislative controls as commercials for broadcast. Manufacturers may seek the Drugs Directorate's opinion on print advertising material before it is used.

Advertisements directed to health professionals in Canadian journals, direct mail pieces, detail ads, audio/visual promotion, and electronic (computer software) promotion are subject to voluntary preclearance by the Pharmaceutical Advertising Advisory Board, a non-governmental board with representation from various professional and manufacturers' associations. The Health Protection Branch maintains an advisory capacity in this process. Although the HPB is in agreement with the objectives of the Board, it maintains the right, under law, to disagree with material directed to health professionals in Canada and to take any action it deems necessary.

# 9. Biologics and Radiopharmaceuticals

## Biologics

Biologics are those drugs listed in Schedule D to the *Food and Drugs Act*. The list includes:

- vaccines,
- blood and blood derivatives,
- certain hormones and enzymes extracted from animal tissues or cultures of microorganisms, and
- drugs produced by modern biotechnology.

The regulatory requirements for drugs listed in Schedule D exceed those for other products; they constitute the most rigorous of controls for safety and effectiveness of all drugs in Canada.

Because the manufacturing processes for these products are intricate and because adherence to standards is critical to the final product, the premises in which biologics are manufactured must be inspected and licensed by the Bureau of Biologics before the products can be sold in Canada. After an initial licence is issued, the premises are regularly inspected, and the licence is renewed annually. Every lot of licensed biologic products must be tested by the Bureau of Biologics before it is distributed for sale.

A drug listed in Schedule D may also be listed in Schedule F. The former schedule regulates how the drug is manufactured and labelled; the latter requires that it be made available to the public only on prescription.

## Radiopharmaceuticals

Radiopharmaceuticals are those drugs listed in Schedule C to the *Food and Drugs Act*. These drugs emit alpha, beta, or electromagnetic radiation and are used primarily for diagnostic procedures and cancer therapy. Schedule C also includes kits for the preparation of radiopharmaceuticals. Because these drugs are radioactive, careful and

exact controls must be implemented in their manufacture and distribution. Thus, the requirements for licensing Schedule D drugs (see "Biologics," above) also apply to radiopharmaceuticals.

The Bureau of Radiation and Medical Devices, Environmental Health Directorate, inspects plants where Schedule C drugs are produced, reviews new drug submissions, and issues the necessary licences. This Bureau maintains its own laboratories for analysing and researching these drugs. The Bureau of Radiation and Medical Devices also acts as principal health advisor to the Atomic Energy Control Board, the agency that controls the use of all radioactive materials, including radiopharmaceuticals.

# 10. Controlled, Restricted, and Narcotic Drugs

Controlled drugs and restricted drugs are listed in Schedules G and H, respectively, to the *Food and Drugs Act*. Narcotic drugs are listed in the Schedule to the *Narcotic Control Act*. These drugs may have habit-forming properties and are also subject to abuse for various reasons.

It is an offence to possess controlled, restricted, and narcotic drugs for the purpose of trafficking. In fact, simply possessing restricted and narcotic drugs for reasons other than those permitted by the *Food and Drugs Act* and the *Narcotic Control Act* is an offence.

In addition to the normal controls placed on all drugs, additional controls are imposed on the manufacture, distribution, and sale of controlled, restricted, and narcotic drugs to prevent their flow from legal to illegal sources. These measures involve:

- licensing dealers,
- keeping record of all drug movement,
- auditing drug records,
- applying import and export controls, and
- co-operating with international drug agencies.

## Licensed Dealers

To manufacture, import, export, sell, or distribute controlled, restricted, or narcotic drugs, dealers must be licensed by the Health Protection Branch. Each month, licensed dealers must report the sale of specific narcotic and controlled drugs.

**Sale of Narcotic and Controlled Drugs by Licensed Dealers**

A licensed dealer may sell narcotic and controlled drugs only to:

- other licensed dealers,
- pharmacists,
- medical practitioners,
- hospitals,

- Regional Directors of the Health Protection Branch, or
- persons authorized by the Minister of National Health and Welfare to possess such drugs.

The sale of methadone and heroin is subject to further restrictions.

## Record Keeping

Licensed dealers must maintain detailed records of all transactions for a minimum of two years. These records must account for:

- all drugs received, their source, and the date received;
- all drugs supplied, to whom they were supplied, and the date they were shipped;
- all drugs manufactured, the quantity produced, and the date of production; and
- a monthly inventory of all stock on hand.

Pharmacists and practitioners must also maintain detailed records of a similar nature about all transactions involving controlled and narcotic drugs.

## Auditing the Records

Inspectors from the Field Operations Directorate audit the records of all licensed dealers, pharmacists, practitioners, and hospitals.

## Import and Export Controls

To import and export controlled, restricted, or narcotic drugs, a licensed dealer in Canada must obtain a permit that states:

- the source of the drug,
- the exact description of the drug,
- the exact quantities imported or exported,
- the destination of the shipment, and
- the port of entry or exit.

### *Single Convention on Narcotic Drugs*

The Bureau of Dangerous Drugs co-operates with international drug enforcement agencies and foreign government units that share the Bureau's areas of interest. The Bureau of Dangerous Drugs

provides quarterly reports, annual reports, and statistics to the International Narcotics Control Board, as required under the United Nations *Single Convention on Narcotic Drugs* (1961).

## Convention on Psychotropic Drugs

Canada became a party to the UN *Convention on Psychotropic Substances* in June of 1987. Canada's accession to the Convention will strengthen international efforts to combat drug abuse and trafficking in various drugs and substances that have the potential for abuse. The Convention will be phased in gradually, starting with legislative/ regulatory amendments, and followed by the extension of departmental programs to carry out the mandate of the Convention.

# Glossary of Terms

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| Addictive | Any substance that tends to induce a physiological or psychological dependency. |
| Adulterate | To corrupt, debase, or make impure by the addition of a foreign or inferior substance. |
| Amphetamines | A group of x-methylphenethylamine drugs used as stimulants of the central nervous system. |
| Antibiotic | A drug that suppresses the growth of microorganisms in the body and helps to control diseases of infectious origin. |
| ASA | Acetylsalicylic acid. |
| Assay | Laboratory analysis to determine the quantity of one or more substances. |
| Barbiturates | A group of drugs derived from barbituric acid, used as sedatives or sleep-inducing agents. |
| Biocomparable pharmaceuticals | Generic drugs or new formulations of a drug from the original manufacturer in which evidence of safety and efficacy is obtained from comparative bioavailability studies in healthy volunteers rather than clinical trials in patients. |
| B.P. | *The British Pharmacopoeia*—a set of drug standards. |
| B.P.C. | *The British Pharmaceutical Codex*—a set of drug standards. |
| C.F. | *The Canadian Formulary*—a set of drug standards. |

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| C.S.D. | *Canadian Standard Drugs*—a *Food and Drugs Act* standard assigned to a specific group of drugs. |
| *Canada Gazette* | A government publication published under Authority of the *Statutory Instruments Act*. It has three parts:<br>Part I Material required by federal statute or regulation to be published in the *Canada Gazette* other than items identified for Parts II and III below—published every Saturday.<br>Part II Statutory Instruments (Regulations) and other classes of statutory instruments and documents—published January 3, 1990 and every second Wednesday thereafter.<br>Part III Public Acts of Parliament and their enactment proclamations—published as soon as is reasonably practicable after Royal Assent. |
| Cosmetic | Any substance or mixture of substances manufactured, sold, or represented for use in cleansing, altering, or improving the complexion, skin, hair, or teeth, including deodorants and perfumes. |
| DIN | Drug Identification Number—an eight-digit, computer-generated number assigned to a specific drug product. |
| Designated Drugs | A group of amphetamine-type stimulant drugs having the potential for abuse, approved for use in the treatment of certain designated diseases in humans and animals. |

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| Drug | Includes any substance or mixture of substances manufactured, sold, or represented for use in (a) the diagnosis, treatment, mitigation, or prevention of a disease, disorder, abnormal physical state, or the symptoms thereof, in humans or animals; (b) restoring, correcting, or modifying organic functions in humans or animals; or (c) disinfection in premises in which food is manufactured, prepared, or kept. |
| Enteric coated | A drug specifically coated to pass through the stomach unaltered and disintegrate in the small intestine; may also be called a delayed-release drug. |
| Epidemiology | The study of the relationships of the various factors that determine the frequency and distribution of diseases in a population. |
| Epilepsy | A disorder marked by disturbed electrical activity of the central nervous system, typically manifested by convulsions and clouding of consciousness. |
| Excipient | A non-medicinal ingredient in a drug product. |
| Expiration date | The earlier of (a) the date until which a drug maintains its labelled potency, purity, or a physical characteristic and (b) the date after which the manufacturer recommends that the drug not be used. |
| GP | "General public"—letters preceding a number assigned to a drug, generally available from any retail outlet, for purposes of identification and registration as a proprietary medicine. |
| Hyperkinetic | Abnormally increased and usually purposeless and uncontrollable muscular movement; "overactive." |

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| IU | International Units—a quantity of a biological compound (e.g., a vitamin) that produces a particular biological effect; agreed upon as an international standard. |
| Identity | The chemical composition that constitutes a drug in its given form. |
| Information Letter (IL) | An HPB publication intended to inform health professionals, manufacturers, consumer associations, and so on, about HPB activities; may contain proposals or decisions on regulatory change or the comments on a previous regulatory proposal, or the reports of Expert Advisory Committees. |
| LSD | Lysergic acid diethylamide—a hallucinogenic drug, subject to abuse, with no accepted medical use; legally available only to institutions involved in highly specialized research. |
| Label | Any legend, word, or mark attached to or accompanying a drug or package; "inner label" is the label on the container; "outer label" is the label on the package of a drug. |
| Limit-Dose Drugs | Drugs available without prescription but for which maximum single or daily dosages are given in the Table to Section C.01.021 of the *Food and Drug Regulations*; dosages exceeding these limits are not suitable for self-medication without the advice of a practitioner. |
| Lot number | Any combination of letters, figures, or both by which any drug can be traced in manufacture and identified in distribution. |
| N.F. | *The National Formulary*—a set of drug standards. |
| Narcolepsy | A condition characterized by uncontrolled brief attacks of sleep occurring at intervals throughout the day. |

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| Narcotic | A term describing a drug that in moderate doses dulls the senses, relieves pain, and induces sleep, but which has a high potential for addiction and abuse. |
| Ophthalmic | Of or relating to the eye. |
| Over-the-counter drugs (OTCs) | Non-prescription drugs intended for self-medication and generally available in pharmacies only. |
| Package | Anything in which a drug, cosmetic, or device is wholly or partly contained, packed, or placed. |
| Parenteral drug | A drug introduced to the body by means other than topical absorption or through the intestinal wall (e.g., intravenous and intramuscular injection). |
| Pathophysiology | The physiology of abnormal states; the functional changes that accompany a particular disease or disorder. |
| pH | A measure of the acidity or alkalinity of a solution. |
| Pharmacodynamics | The branch of pharmacology dealing with the actions of drugs on living organisms, including the correlation of their action with their chemical structure. |
| Pharmacoepidemiology | The study of the use of and effects of drugs in large numbers of people. Pharmacoepidemiology is a combination of the relevant aspects of epidemiology with pharmacology. |
| Pharmacokinetics | The study of the absorption, distribution, metabolism, and excretion of drugs by the body. |
| Ph.F. | *Pharmacopée Française*—a set of drug standards. |
| Ph.I. | *Pharmacopoeia Internationalis*—a set of drug standards. |
| Potency | Quantitative measure of a medicinal or active ingredient in a product. |

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| Practitioner | A person who is registered and entitled under the laws of a province to practice, in that province, the profession of medicine, dentistry, or veterinary medicine. |
| Prescribing information | Information taken from the product monograph and provided to health professionals as part of the promotional and advertising material. |
| Prescription | An order given by a practitioner, directing that a stated amount of a drug or mixture of drugs specified therein be dispensed for the person named in that order. |
| Product monograph | Factual, scientific document about the drug product, devoid of promotional material, describing the properties, claims, indications, and conditions of use of the drug and containing any other information that may be required to provide adequate direction for the drug's safe and effective use. |
| Psychoactive | A compound that has the ability to modify mental activities and affect mood, thinking, perceptions, and often behaviour; also known as psychotropic. |
| Purity | The absence of foreign substances in a drug. |
| Pyrogen | A fever-producing substance. |
| Residue | A remainder; that which remains after the removal of other substances. |
| Standard | A criterion set up and established by authority as a rule for the measure of quality, weight, value, or quantity. |
| Schedule drugs | Drugs listed in the Schedule to the *Narcotic Control Act*, Schedule G or H of the *Food and Drugs Act*, and Schedule F of the *Food and Drug Regulations*. |

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| Security package | A package having a security feature that provides reasonable assurance to consumers that the package has not been opened prior to purchase. |
| Synthetic | Chemical compound built up in a laboratory by the fusing of its various elements; possesses the same molecular structure as its corresponding naturally occurring compound, where a naturally occurring compound exists. |
| Therapeutic use | Vitamins or minerals containing this caution are used in the treatment of conditions that a member of the general public cannot accurately self-diagnose (i.e., the advice of a practitioner is necessary). Advertising of such products to the general public is restricted to name, price, and quantity. |
| U.S.P. | *United States Pharmacopeia*—a set of drug standards. |
| Withdrawal (or withholding) time | The period of time after drug treatment that a residue remains in animal tissues; observing this period avoids harmful drug residues remaining in meat, milk, or eggs. |

# Other Publications for Reference

The publications listed below should be used in conjunction with, or to supplement, the information contained in this booklet.

## Acts and Regulations

The *Food and Drugs Act*

The *Food and Drug Regulations*

The *Narcotic Control Act*

The *Narcotic Control Regulations*

## Dispatches (Field Operations Directorate)

Canadian Drug Laws and the Consumer—Dispatch No. 33.

Cosmetic Safety and the Consumer—Dispatch No. 40.

Food and Drug Interactions—Dispatch No. 50.

Drug Interactions—Dispatch No. 56.

Analgesics—Dispatch No. 59.

## Drugs Directorate Guidelines

The following is a list of Drugs Directorate Guidelines that have been, or are soon to be, published.

**Drugs for Human Use**

Chemistry and Manufacturing: New Drugs

Completing an Application for Registration as a Proprietary Medicine

Conduct and Analysis of Comparative Bioavailability Studies

Conduct of Clinical Investigations

Dependence Liability

Good Manufacturing Practices (GMP)

Preparation of Human New Drug Submissions

Preparation of Investigational New Drug Submissions

Product Master Files

Product Monographs

Stability

Toxicologic Evaluation

**Drugs for Veterinary Use**

Preparation of Veterinary New Drug Submissions

**Labelling and Advertising**

Consumer Drug Advertising

Labelling of Drugs for Human Use

**Cosmetics**

Labelling of Cosmetics

**Biologics**

Blood Collection

Manufacture and Testing of Biologics Produced by Recombinant DNA Technology

Manufacture and Testing of Monoclonal Antibodies and Their Conjugates

Utilization of Continuous Cell Lines in the Manufacture of Biologics

**Other**

Disinfectants: Preparation of Application for Drug Identification Numbers

Homeopathic Preparations: Application for Drug Identification Numbers

Traditional Herbal Medicines

## Drugs Directorate Publications

Drugs Directorate Questions and Answers

Open Arms and Alternative Clinical Trial Designs

Report of the Expert Advisory Committee on Amino Acids

Risk-Benefit and Quality-of-Life Analyses of Prescription Drugs

Risk Perception and Drug Safety Evaluation

## Laboratory Centre for Disease Control Publications

Emergency Treatment of Poisoning

Poison Control Program Statistics

## Field Operations Directorate Leaflets and Information Letters

How to Lodge a Complaint Effectively

Product Recall Procedures (HPB Information Letter No. 661)

Protection is Our Middle Name

## Other Health and Welfare Canada Publications

Health and Welfare Canada, 1985. *Guidelines for the Preparation of Drug Submissions on Schedule C Drugs* 85-EHD-122.

## Journal Articles

Morrison, A. B., "The Canadian Approach to Food and Drug Regulations," *Food, Drug, Cosmetic Law Journal* 30 (1976):632–643.

Somers, E., Carman Kasparek, M., and Pound, J., "Drug Regulation—The Canadian Approach," *Regulatory Toxicology and Pharmacology* 12 (1990):214–223.

# Health Protection Branch Offices

More information on the Health Protection Branch, its activities, and Canada's drug laws, may be obtained by contacting the headquarters office in Ottawa or any of the five regional offices shown below.

## Main Office

Health Protection Branch
Health and Welfare Canada
Tunney's Pasture
OTTAWA, ON
K1A 0L2

## Regional Offices

Health Protection Branch
Suite 601
Park Lane Terrace
5657 Spring Garden Road
HALIFAX, NS
B3J 3R4

Health Protection Branch
1001 St. Laurent Blvd. West
LONGUEUIL, PQ
J4K 1C7

Health Protection Branch
2301 Midland Avenue
SCARBOROUGH, ON
M1P 4R7

Health Protection Branch
510 Lagimodière Blvd.
WINNIPEG, MB
R2J 3Y1

Health Protection Branch
3155 Willingdon Green
BURNABY, BC
V5G 4P2